G9a functions as a molecular scaffold for assembly of transcriptional coactivators on a subset of glucocorticoid receptor target genes.

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Public Summary:
Glucocorticoid (GC) steroids are the most effective therapeutic agents in clinical use for treating diseases involving chronic inflammation. However, their beneficial anti-inflammatory activity is inextricably linked to myriad adverse effects including osteoporosis, diabetes, central obesity, adrenal suppression, hypertension, muscle wasting, skin atrophy, mood disturbances, and insomnia. This is due to the fact that GC treatment results in the activation or repression of a wide variety of genes. Characterizing which proteins activate/repress distinct pathways (anti-inflammatory, osteoporosis, etc...) of the GC response could help in identifying therapeutic targets to limit the adverse effects of GCs. G9a is a key protein implicated in the regulation of gene expression. Unlike most proteins which either activate or repress genes, G9a is a “switch” that can (through an unknown mechanism) both activate and repress genes. We did a global analysis of gene expression in response to GC treatment and we show that: i. G9a helps GCs to activate a specific subset of genes and to repress a different subset of genes; ii. G9a helped to repress GC target genes through its enzymatic activity; iii. G9a enzymatic activity was not required for its activation function. Instead, G9a helped to activate GC target genes by serving as a scaffold for the assembly of a complex of activator proteins on the gene; iv. G9a enzymatic activity inhibitors can abolish G9a-mediated repression of genes while maintaining G9a-mediated activation of genes. Overall, these findings indicate distinct mechanisms of G9a activator vs. repressor functions. Our results also suggest a physiological role of G9a in fine tuning the set of genes that respond to GCs.

Scientific Abstract:
Histone H3 lysine-9 methyltransferase G9a/EHMT2/KMT1C is a key corepressor of gene expression. However, activation of a limited number of genes by G9a (independent of its catalytic activity) has also been observed, although the precise molecular mechanisms are unknown. By using RNAi in combination with gene expression microarray analysis, we found that G9a functions as a positive and a negative transcriptional coregulator for discrete subsets of genes that are regulated by the hormone-activated Glucocorticoid Receptor (GR). G9a was recruited to GR-binding sites (but not to the gene body) of its target genes and interacted with GR, suggesting recruitment of G9a by GR. In contrast to its corepressor function, positive regulation of gene expression by G9a involved G9a-mediated enhanced recruitment of coactivators CARM1 and p300 to GR target genes. Further supporting a role for G9a as a molecular scaffold for its coactivator function, the G9a-specific methyltransferase inhibitor UNC0646 did not affect G9a coactivator function but selectively decreased G9a corepressor function for endogenous target genes. Overall, G9a functioned as a coactivator for hormone-activated genes and as a corepressor in support of hormone-induced gene repression, suggesting that the positive or negative actions of G9a are determined by the gene-specific regulatory environment and chromatin architecture. These findings indicate distinct mechanisms of G9a coactivator vs. corepressor functions in transcriptional regulation and provide insight into the molecular mechanisms of G9a coactivator function. Our results also suggest a physiological role of G9a in fine tuning the set of genes that respond to glucocorticoids.

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